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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/529,352	01/11/2006	Nigel Tooke	21465-523 NATL	2533

35437 7590 06/09/2009

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EXAMINER	
WOOLWINE, SAMUEL C	
ART UNIT	PAPER NUMBER
1637	
MAIL DATE	DELIVERY MODE
06/09/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/529,352	TOOKE, NIGEL	
	Examiner	Art Unit	
	SAMUEL WOOLWINE	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 March 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7,9-11,14-18,20 and 23-35* is/are pending in the application.

4a) Of the above claim(s) *9-11 and 27-35* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7,14-18,20 and 23-26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12/12/2008;03/242/2009*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status

Applicant's amendment filed 03/12/2009 is acknowledged. Presently, claims 1-7, 9-11, 14-18, 20, 23-35 are pending in the application. Claims 9-11, 27-35 remain withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention and/or species, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 09/25/2007.

The rejections made under 35 U.S.C. 112, 1st (new matter) and 2nd paragraphs in the Office action mailed 12/10/2008 are withdrawn in view of Applicant's amendments.

New grounds of rejection are set forth below which were necessitated by Applicant's amendment. As stated in the 12/10/2008 Office action (page 6), Applicant's arguments in the response filed 09/12/2008 will be addressed to the extent they apply to the rejections set forth below.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-7 and 14-19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ronaghi (WO 00/43540, prior art of record) in view of Kotewicz et al (US 5,244,797, prior art of record), Inouye (US 5,434,070, prior art of record) and Wilkinson et al (GB2351559, published January 3, 2001, prior art of record).

Ronaghi teaches a method of sequencing nucleic acids by pyrophosphate sequencing (i.e. "pyrosequencing").

With regard to claim 1, Ronaghi teaches *a method for determining the identity of at least one nucleotide in a RNA-molecule*

See page 1, first paragraph: "The present invention relates to methods of nucleic acid sequencing..."; page 5, first paragraph: "The nucleic acid may be DNA or RNA..."; page 5, last full paragraph: "In the case of a RNA template, such a polymerase may be a reverse transcriptase enzyme."

comprising the steps of:

(a) providing a single stranded form of the RNA-molecule

Ronaghi teaches that the nucleic acid being sequenced can be RNA as discussed above. For example, Ronaghi teaches mRNA (page 12, first paragraph), which is inherently single stranded.

(b) hybridising an oligonucleotide primer binding to a predetermined position of the RNA molecule

See page 4, last full paragraph: "...wherein a primer, which hybridises to the sample nucleic acid immediately adjacent to the target position, is provided...".

(c) performing at least one primer extension reaction in an extension reaction solution comprising reagents to detect light triggered by the release of PPi

See page 8, beginning at third full paragraph: "...methods which rely on monitoring the release of inorganic pyrophosphate (PPi) are particularly preferred. In this case, incorporation of the nucleotide will be measured indirectly by enzymatic

detection of released PPi." See also page 8, last paragraph and entire page 9, where Ronaghi teaches luciferin, luciferase, ATP sulphurylase, which are reagents to detect light triggered by the release of PPi.

and a RNA-secondary structure reducing reagent

See page 4, last full paragraph: "the present invention thus provides a method…characterized in that, a single-stranded nucleic acid binding protein is included in the polymerase reaction step." See also page 7, first full paragraph, where Ronaghi lists single-stranded nucleic acid binding proteins including T4 gene 32 protein and SSB. Ronaghi also teaches DMSO and formamide (top of page 16). Each of these is specifically recited in Applicant's specification as exemplary RNA-secondary structure reducing reagents.

whereby the oligonucleotide primer is extended on the RNA-molecule through incorporation of at least one nucleotide by the action of a RNA dependent polymerase, whereby the polymerase is a reverse transcriptase

See page 5, last full paragraph: "In the case of a RNA template, such a polymerase enzyme may be a reverse transcriptase enzyme."

(d) detecting the presence or absence of incorporation, thereby indicating the nucleotide identity of the RNA molecule in the relevant position

See page 6, last paragraph: "…detecting the presence or absence of incorporation…".

whereby step (c) to (d) optionally are repeated

See page 6, last paragraph: "Hence, a sequencing protocol may involve annealing a primer as described above, performing a polymerase-catalysed primer extension step, detecting the presence or absence of incorporation, and repeating the nucleotide addition and primer extension steps etc. one or more times."

In addition, Ronaghi teaches dATPαS analog in place of dATP (page 13, last full paragraph).

With regard to claim 2, see last statement regarding claim 1.

With regard to claim 4, Ronaghi teaches released PPi, which is a detectable moiety, to indicate the presence or incorporation (page 8, third full paragraph: "incorporation of the nucleotide will be measured indirectly by enzymatic detection of released PPi").

With regard to claim 5, the PPi is neutralized or removed via conversion into ATP by ATP sulphurylase, which ATP is then hydrolyzed by luciferase to produce light (see reaction, page 9).

With regard to claims 6 and 7, PPi is a residue molecule released by the primer extension reaction (i.e. the incorporation of a nucleotide; see statement regarding claim 4).

Ronaghi does not teach that the hybridization is performed in the presence of at least one RNAse-inhibiting agent, or a mixture of the types of reverse transcriptases recited in claim 1.

Ronaghi does not teach "recording" as recited in claim 3.

Ronaghi does not teach the temperature, pH, nucleotide concentration, or salt concentration limitations as recited in claims 14-17, respectively.

With regard to claim 18, while Ronaghi teaches primers, he does not explicitly indicate the primers were DNA primers.

Kotewicz teaches a method for synthesizing cDNA from an RNA template using a reverse transcriptase.

With regard to claim 1, Kotewicz teaches a reverse transcriptase that lacks RNase H activity (column 2, lines 49-51). Kotewicz's enzyme is a M-MuLV reverse transcriptase (column 11, lines 9-15; M-MLV is the same as M-MuLV).

With regard to claim 14, Kotewicz uses this enzyme to perform primer extension from an RNA template at 37°C (column 14, lines 17-18).

With regard to claim 15, Kotewicz uses this enzyme to perform primer extension from an RNA template at pH 8.3 (column 14, line 13).

With regard to claim 16, Kotewicz uses this enzyme to perform primer extension from an RNA template at a nucleotide concentration of 0.5 mM (column 14, lines 14-15).

With regard to claim 17, Kotewicz uses this enzyme to perform primer extension from an RNA template at salt (KCl) concentration of 75 mM (column 14, line 13).

With regard to claim 18, Kotewicz uses this enzyme to perform primer extension from an RNA template using a DNA primer $(dT)_{12\text{-}18}$ (column 14, lines 17-18).

With regard to claim 1, Inouye teaches at column 12, line 66 through column 13, line 9 (emphasis provided):

"For background and protocols on synthesis of cDNA and reverse transcript, see Molecular Cloning: A Laboratory Manual ("Maniatis") pages 129-130 and 213-216 (incorporated herein by reference). If it is desired to separate any RNase activity when such is present, the protocols referred to in Maniatis in the Chapter on Synthesis of cDNA may be referred to (page 213). See also Marcus et al., J. Virol., 14, 853 (1974) and other references cited at page 213. Other protocols are known in the art, such as including in the reverse transcription reaction mixture an inhibitor of RNase, such as vanadyl-ribonucleoside complexes or RNasin."

With regard to claim 1, Wilkinson teaches using a mixture of reverse transcriptases (specifically a mixture of avian myeloblastosis virus (AMV) reverse transcriptase and Moloney murine leukemia virus (M-MuLV) reverse transcriptase) to increase the sensitivity and product yield of reverse transcription (see abstract and page 5, lines 7-10, for example). Note that instant claim 1 recites AMV RT as a reverse transcriptase that essentially lacks RNase H acitivity.

With regard to claim 1, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to use the reverse transcriptase essentially lacking RNase H activity taught by Kotewicz for the purpose of sequencing an RNA molecule by the method of Ronaghi. One would have been motivated to do so,

because Kotewicz teaches that RNase H activity is a major problem when using reverse transcriptase to synthesize cDNA (column 1, line 47 through column 2, line 5). cDNA synthesis is precisely what would occur in the embodiment of sequencing taught by Ronaghi at page 5, last full paragraph: "In the case of a RNA template, such a polymerase enzyme may be a reverse transcriptase enzyme." One of ordinary skill in the art would have realized that the same problem taught by Kotewicz with regard to synthesizing cDNA would also have existed in the RNA sequencing embodiment taught by Ronaghi, and would therefore have been motivated to use a reverse transcriptase lacking RNase H activity.

It would also have been *prima facie* obvious to use an RNase inibitor when practicing the RNA sequencing method suggested by the combined teachings of Ronaghi and Kotewicz, since it was known in the art that RNA was susceptible to RNase degradation, and Inouye teaches it was known in the art, in the context of a reverse transcriptase reaction, to add inhibitors of RNase.

It would also have been *prima facie* obvious to use a primer made of DNA when reverse transcribing an RNA template, as Kotewicz demonstrates this was common practice. Indeed, absent any particular teachings to the contrary in Ronaghi, one of skill would have assumed the primers used in the sequencing reaction were made of DNA as sequencing reactions, reverse transcription reactions, PCR reactions all typically employed DNA primers.

It would also have been *prima facie* obvious to use a mixture of reverse transcriptases as proposed by Wilkinson in order to achieve the improvement in

sensitivity and yield taught by Wilkinson. In addition, even without an expectation increased yield taught by Wilkinson, it would have been obvious to combine different reverse transcriptases as Wilkinson did because it is *prima facie* obvious to combine equivalents known for the same purpose (MPEP 2144.06 (I)).

With regard to claims 14-18, it would have been obvious to use the conditions of temperature, pH, salt and nucleotide concentrations, and to use a DNA primer (thus meeting the limitations of claims 14-18), since Kotewicz had shown these to be appropriate conditions for synthesis of DNA from an RNA template using reverse transcriptase.

With regard to claim 3, while the cited references do not expressly teach or suggest recording the nucleotides incorporated, it would have been obvious to one of skill in the art to do so. Otherwise, one practicing the method would have had to commit to memory the sequence in which nucleotides were incorporated (which, incidentally, would still be "recording"). What would have been the purpose of sequencing a nucleic acid molecule and *not* recording the results?

Claim 20 is rejected under 35 U.S.C. 103(a) as being unpatentable over Ronaghi (WO 00/43540, prior art of record) in view of Kotewicz et al (US 5,244,797, prior art of record), Inouye (US 5,434,070, prior art of record) and Wilkinson et al (GB2351559, published January 3, 2001, prior art of record) as applied to claims 1-7 and 14-19 above, and further in view of Blasband et al (US 6,451,525).

The teachings of Ronaghi, Kotewicz, Inouye and Wilkinson have been discussed. These references do not teach using an RNA primer.

Blasband teaches a method for parallel sequencing of target polynucleotides in a sample (see abstract). With regard to claim 20, Blasband teaches (column 9, lines 15-21): "In one embodiment, the primer extending reagent is a DNA polymerase enzyme. Exemplary polymerase enzymes include, but are not limited to, Pfu DNA polymerase, E. coli polymerase I, T-7 polymerase, reverse transcriptase, Taq DNA polymerase, TAQ FS polymerase, and the like (Kornberg and Baker). RNA polymerases and reverse-transcriptases can also be used, e.g., for RNA primers."

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention of the instant application was made to use either DNA or RNA as the primer when practicing the method for sequencing RNA suggested by the combined teachings of Ronaghi, Kotewicz, Inouye and Wilkinson, since both were known in the prior art to be suitable for primer extension by reverse transcriptase in nucleic acid sequencing methods. See MPEP 2144.07 regarding the selection of a known material based on its suitability for its intended purpose.

Claims 23 and 24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ronaghi (WO 00/43540, prior art of record) in view of Kotewicz et al (US 5,244,797, prior art of record), Inouye (US 5,434,070, prior art of record) and Wilkinson et al (GB2351559, published January 3, 2001, prior art of record) as applied to claims 1-7 and 14-19 above, and further in view of Malek et al (US 5,665,545, prior art of record).

The teachings of Ronaghi, Kotewicz, Inouye and Wilkinson have been discussed. These references do not teach amplifying the RNA prior to sequencing or using rITP in place of rGTP during amplification of the RNA.

Malek teaches a method of amplifying RNA called TRAM (terminal repeat amplification method) and teaches that substitution of rITP for rGTP in an RNA amplification product alleviates pausing of reverse transcriptase due to secondary structure (stem-loop formation) when using the RNA in a subsequent primer extension reaction (column 24, lines 21-45).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention of the instant application was made to use the known method of RNA amplification taught by Malek when practicing the method for sequencing RNA suggested by the combined teachings of Ronaghi, Kotewicz, Inouye and Wilkinson, since Ronaghi teaches the desirability of amplifying the nucleic acid to be sequenced (page 10, lines 1-4). Furthermore, it would have been obvious to exchange rITP for rGTP to produce an RNA amplification product, as Malek shows that such a product reduces pausing of the reverse transcriptase during primer extension. Primer extension mediated by reverse transcriptase was what was taught by Ronaghi at page 5, last full paragraph: "In the case of a RNA template, such a polymerase enzyme may be a reverse transcriptase enzyme."

Claims 25 is rejected under 35 U.S.C. 103(a) as being unpatentable over Ronaghi (WO 00/43540, prior art of record) in view of Kotewicz et al (US 5,244,797,

prior art of record), Inouye (US 5,434,070, prior art of record) and Wilkinson et al (GB2351559, published January 3, 2001, prior art of record) as applied to claims 1-7 and 14-19 above, and further in view of Williams et al (US 2002/0137062).

The teachings of Ronaghi, Kotewicz, Inouye and Wilkinson have been discussed. Ronaghi taught that in order to repeat the method cyclically, it would be desirable to immobilize the sample nucleic acid on a solid support (page 9, last paragraph). The cited references do not teach capturing RNA to a solid support by way of a primer immobilized on the solid support in order to sequence the RNA.

Williams teaches methods of sequencing nucleic acids (see abstract) including mRNA, and teaches capturing the RNA to a solid support using a primer thereto (paragraph [0044]):

"In addition, reverse transcriptase which catalyzes the synthesis of single stranded DNA from an RNA template may be utilized in the reactive sequencing method of the invention to sequence messenger RNA (mRNA). Such a method comprises sequentially contacting an RNA template annealed to a primer (RNA primer/template) with dNTPs in the presence of reverse transcriptase enzyme to determine the sequence of the RNA. Because mRNA is produced by RNA polymerase-catalyzed synthesis from a DNA template, and thus contains the sequence information of the DNA template strand, sequencing the mRNA yields the sequence of the DNA gene from which it was transcribed. Eukaryotic mRNAs have poly(A) tails and therefore the primer for reverse transcription can be an oligo(dT). Typically, it will be most convenient to synthesize the oligo(dT) primer with a terminal biotin or amino group through which the primer can be

captured on a substrate and subsequently hybridize to and capture the template mRNA strand."

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to use the technique taught by Williams for capturing mRNA to a solid support for sequencing by the method suggested by the combined teachings of Ronaghi, Kotewicz, Inouye and Wilkinson since both Ronaghi and Williams teach immobilizing sequencing templates to solid supports for the purpose of sequential (i.e. cyclical) addition of sequencing reagents (dNTPs) (see Williams, paragraph [0049]), both Ronaghi and Williams teach sequencing RNA templates using reverse transcriptase, and since Williams provides a means for attaching RNA sequencing templates to solid supports. The basic distinction between Ronaghi and Williams is that Ronaghi teaches detecting sequential incorporation of nucleotides by PPi release, Willaims teaches detection by such techniques as microcalorimetry, or fluorescent or chemiluminescent detection of modified nucleotides (see paragraph [0014]).

Claim 26 is rejected under 35 U.S.C. 103(a) as being unpatentable over Ronaghi (WO 00/43540, prior art of record) in view of Kotewicz et al (US 5,244,797, prior art of record), Inouye (US 5,434,070, prior art of record) and Wilkinson et al (GB2351559, published January 3, 2001, prior art of record) as applied to claims 1-7 and 14-19 above, and further in view of Lundeberg et al (US 2003/0157499).

The teachings of Ronaghi, Kotewicz, Inouye and Wilkinson have been discussed. These references do not teach determining "a quantity" of the RNA molecule by measuring the intensity of the incorporation signal and comparing it to a reference.

Lundeberg teaches (paragraph [0042]):

"The pyrophosphate detection step results in a signal indicative of the amount of pyrophosphate released. It has been confirmed that this signal is proportional to the amount of template present i.e. amplicons derived from target or competitor and therefore the signal is proportional to the number of target and competitor molecules originally present. If the amount of competitor is known, it follows that the amount of target can be calculated. Preferably, a calibration curve based on detection of extension reactions from competitor templates is generated and this can be used to read off quantitative information regarding the amount of target nucleic acid present in the sample. There is a linear correlation between the signal (i.e. the amount of PPi released) and the relative amount of template."

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to modify the method suggested by the combined teachings of Ronaghi, Kotewicz, Inouye and Wilkinson by assessing the quantity of the template in the sample by comparing the amount of pyrophosphate by the sequencing sample to a calibration curve established using known concentrations of templates, as Lundeberg teaches there is a linear correlation between the amount of PPi released and the amount of template. One would have been motivated to do this in order to obtain information as to the quantity of the target nucleic acid in the sample.

Response to Arguments

Applicant's arguments filed 09/12/2008 have been fully considered but they are not persuasive. Applicant argued beginning on page 9 against the rejections made over Ronaghi in view of Kotewicz and Inouye. Applicant argued that these references did not teach or suggest a mixture of reverse transcriptases, nor did they teach a primer wherein the primer comprised dATP or ATP that had been replaced with alpha-S analogs. These arguments are moot since the pending rejections also rely on Wilkinson, who provides a motivation to use a mixture of reverse transcripases, and since the claims no longer require a primer comprising alpha-S analogs (rather, the claims require a primer extension reaction comprising these analogs, such that they are incorporated into an extended primer; this limitation has been accounted for in the instant rejections).

As to Applicant's arguments on pages 11-12 of the response regarding the rejection of [now cancelled] claim 13, which relied on Wilkinson to provide motivation to use a mixture of reverse transcriptases, Applicant has argued:

> The Wilkinson mixture of reverse transcriptases are presumed to contain substantial RNase H activity. There is no explicit disclosure in Wilkinson that the reverse transcriptase mixture comprises RNase H activity, but Wilkinson does disclose at page 3, lines 10-15 that, "[t]raditionally, only one reverse transcriptase, for example either AMV or MMuLV,

has been used to catalise first strand synthesis in the RT-PCR reaction. Each is characterized by distinct RNase H activities and temperature and pH optima. Principally, AMV possesses higher levels of RNase H activity relative to MMuLV, which is responsible for the degradation of the RNA in the RNA:DNA hybrids." This disclosure suggests that, while AMV and MMuLV have different RNase H activities, retaining RNase H activity in the practice of the Wilkinson invention is preferred. There is also no indication from the Wilkinson disclosure that the AMV and MMuLV are mutated in any way from the wild-type enzyme, which those skilled in the art would recognize as having RNase H activity.

This argument is not persuasive. As an initial matter, instant claim 1 does not require the reverse transcriptase to be "mutated", but merely requires a mixture of reverse transcriptases that "essentially lack" RNase H activity, and clearly recites AMV RT as such an enzyme (in addition to "AMV RT mutant completely lacking RNase H activity").

Secondly, there is no explicit definition or upper limit in the specification describing how much RNase H activity a reverse transcriptase may have and still "essentially lack RNase H activity".

Thirdly, Wilkinson does not teach or suggest that RNase H activity is required for the beneficial effects of the mixture and does not teach or suggest that retention of RNase H activity is "preferred". In fact, Wilkinson does not propose any particular mechanism for the unexpectedly increased yield of the mixture. However, as the activity of RNase H is to degrade RNA in an RNA:DNA duplex (see Wilkinson page 3, line 14), one would not have expected such activity to be responsible for increased yield of cDNA product, since (a) this activity would only manifest *after* the cDNA had been synthesized to create an RNA:DNA duplex, and (b) the degradation of the RNA in a

particular RNA:DNA duplex would prevent any additional cDNA synthesis using that particular RNA molecule. Moreover, even if RNase H activity *were* required (or expected to be required) to achieve the increased yield, it would still have been obvious to combine different reverse transcriptases for the purpose of reverse transcription since it is *prima facie* obvious to combine equivalents known for the same purpose, as discussed in the rejection (MPEP 2144.06 (I)).

Finally, Kotewicz provided a clear motivation to use RNase H^- reverse transcriptase because Kotewicz taught that RNase H activity was a major problem when using reverse transcriptase to synthesize cDNA (column 1, line 47 through column 2, line 5).

With regard to Applicant's arguments over the rejection of claims 23 and 24 over the additional disclosure of Malek, Applicant rightly describes the RNA amplification method of Malek as relying on RNase H activity. However, it is noted that claim 23 recites "whereby the RNA molecule is subject to an RNA amplification prior to the extension reaction". The "extension reaction" corresponds to the method disclosed by Ronaghi for using reverse transcriptase to sequence an RNA template. The disclosure of Kotewicz provides the motivation to use a reverse transcriptase devoid of RNase H activity when reverse transcribing cDNA. There is nothing inconsistent about using Malek's method of amplifying RNA (which utilized RNase H activity) *prior to* carrying out the extension (i.e. sequencing) reaction using reverse transcriptases lacking RNase H activity.

With regard to Applicant's arguments over the rejections relying on the additional disclosures of Myers and Rothberg, these arguments are moot as these references are no longer relied upon in the instant rejections.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SAMUEL WOOLWINE whose telephone number is (571)272-1144. The examiner can normally be reached on Mon-Fri 9:00am-5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571) 272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Samuel Woolwine/
Examiner, Art Unit 1637

/Young J Kim/
Primary Examiner, Art Unit 1637